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10/713,008	11/17/2003	Masaaki Ikeda	64517.000002	5744

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,008	IKEDA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-31* is/are pending in the application.

4a) Of the above claim(s) *7-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6 and 16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/06/07 has been entered.

For the purposes of prosecution, the following is defined:

2. The specification fails to define "proliferation." The specification teaches the presence of the proliferation marker Ki-67 is an indicator of proliferation as only present during certain cell cycle phases, but this increase in Ki-67 is not necessarily in parallel with an increase in cell number (see in vitro data versus in vivo data) (see examples). The specification also teaches that cardiomyocytes in vitro are capable of increasing cell number, thus "proliferating" cardiomyocytes (see in vivo data). Thus, using the broadest reasonable interpretation in light of the instant specification the term "proliferating" reads on any marker associated with the cell cycle, or an increase in cell number.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 4, 18, 21, 23, and 24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1, 4, 18, 21, 23, and 24 read on a method for proliferating cardiomyocytes comprising introducing a mammalian D1 cyclin and mammalian Cdk4 kinase into the nucleus of the cells, and cultivating or holding the cells. The claims, as written, do not sufficiently distinguish the natural method of expression and cellular locations of Cdk4/Cyclin D complexes in cardiomyocytes as they exist naturally during development because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Moore et al (Nuclear Import of Cdk/Cyclin Complexes: Identification of Distinct Mechanisms for import of Cdk2/Cyclin E and Cdc2/Cyclin B1. The Journal of Cell Biology, 1999. 114(2):213-224) teaches that most cyclin-dependent kinase/cyclin complexes are localized to the nucleus when active (see abstract). Moore teaches that studies have shown that mutant forms of cyclin D1 can prevent cdk4 from localizing to the nucleic, and that the Cdk/cyclin inhibitor p21, was able to restore Cdk4/cyclin D1 nuclear localization when co-overexpressed with the mutant cyclin D1 (see page 214, right column, last paragraph). The specification defines the term "hold" as "to maintain said cells or said tissues in the physiological conditions such as body temperature and bloodstream without loss of physiological function thereof" (see page 14 of the instant specification). Thus the term "hold" reads on the physiological conditions of a cardiomyocyte in vivo. In the absence of the hand of man, the naturally occurring methods are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should

be amended to indicate the hand of the inventor, e.g., by insertion of "heterologous" or "transgene" or "recombinant". See MPEP 2105.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 4, 6,16-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes in vitro by introducing adenoviral vectors expressing a D-type cyclin, CDK4 or CDK 6 and a nuclear localization signal, does not reasonably provide enablement for an in vivo method of proliferating any cardiomyocyte by introducing any D-type cyclin and either CDK 4 or CDK 6 into the cardiomyocyte. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

6. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter.,

1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

7. 1) The nature of the invention. The invention involves a method of proliferating cardiomyocytes comprising adding a gene encoding a mammalian cyclin D1 gene and NLS fusion protein and a mammalian CDK4 or CDK6 gene into cardiomyocytes in vitro, or introducing the genes directly to cardiomyocytes in vivo, using a viral vector including adenoviral vectors.

8. 2) State of the art. The art shows the over expression of mammalian cyclin D1 and/or CDK4 or CDK 6 causes cardiomyocyte proliferation is well known in the art at the time of the invention (see the Cyclin D1 transgenic mice in Soonpaa et al (Cyclin D1 overexpression Promoter Cardiomyocyte DNA synthesis and Multinucleation in Transgenic Mice. Journal of Clinical Investigation, 1997: 99(11):2644-2654). Soonpaa teaches that future therapeutic uses of heart-specific cyclin D and cdk4 over expression may be used for cardiac regeneration in many forms of cardiovascular disease conditions. It is also well known that the heterologous expression via a baculovirus vector into in vitro insect cells results in expression of the transgenes (see US Patent 6,180,763). The addition of nuclear localization signals to heterologous CDK4 molecules is also well known in the art at the time of the invention (See Paterson et al (US Patent 7,256,256)). It is also well known that active cyclins and cdk complexes, including Cdk4/cyclin d are transported to the nucleus. However, what is not known is the success of *in vivo* gene transfer of two heterologous constructs from a viral vectors including adenoviral vectors in vivo capable of proliferating quiescent cardiomyocytes.

9. Patel et al (Safety of Direct Myocardial Administration of an Adenovirus Vector Encoding Vascular Endothelial Growth Factor 121, Human Gene Therapy .10:1331-1348) publishes the studies that resulted in human clinical trials, of adenoviral gene transfer to hearts in animal models. These data provide information on the safety of the methodology, not necessarily on the "success" of the therapy. Furthermore, Patel teaches that the results do not necessarily equate to success in humans, and factors such as cytotoxiticity, adenoviral concentrations, and long term effects on the models are necessary, to even consider the animal model a "potential gene therapy" (see abstract). Patel provides a model in which the adenoviral vectors are directly injected into the myocardium of genes, only in disease tissue areas, with known concentrations, and assesses the animal by survival, serial echocardiography, blood analysis, and histology sections (see abstract). Intramyocardial injection of the adenoviral vectors cause some inflammation and necrosis (see abstract). Control mice (used to compare administration intravenously against the pig samples) who had high doses of the adenovirus administered intravenously died at the highest adenovirus concentrations (see abstract). Thus the art teaches that myocardial administration of adenoviral vectors is a complex process, with many factors, conditions and issues to be addressed, in order to consider the method for therapeutic potential.

10. 3) Unpredictability of the art. The art is highly unpredictable. Tamamori-Adachi et al (Expression of cyclin D1 and CDK4 causes hypertrophic growth of cardiomyocytes in culture: a possible implication for cardiac hypertrophy. Biochemical and Biophysical

Research Communications, 2202. 296:274-280) teaches that the administration of ectopic cyclin D and cdk4 causes cardiomyocyte hypertrophy in vitro.

Nicol et al (From The Sarcomere To The Nucleus: Role of Genetics and Signaling in Structural Heart Disease, Annual Review of Genomics and Human Genetics, 2000. 1: 179-223) teaches that hypertrophic cardiomyopathies result in heart failure, the genetic and mechanistic causes are complicated and unknown, and ultimately lead to heart failure. Nicol states:

The heart is a unique organ, in that about 3 billion cycles of coordinated contraction and relaxation are required over the lifetime of an average human to maintain the blood supply of the entire organism. Tight control of the cardiomyocyte's genetic program and the ability to adapt to various physiological and pathophysiological stimuli are therefore of critical importance. Primary and acquired structural heart diseases are the leading causes of morbidity and mortality in the industrialized world. The most common forms of acquired structural heart disease are myocardial infarctions due to coronary artery disease and hypertensive cardiomyopathy. However, there is increasing evidence that monogenetic causes of cardiomyopathies are more frequent than previously recognized (76, 148). Surprisingly, the disease progression observed in cardiomyopathies of these seemingly unrelated origins is remarkably similar. So what is the connection?
11. Both intrinsic contractile deficits and extrinsic stresses can compromise cardiac function (Figure 1). Invariably the heart attempts to maintain normal contractile function and output by undergoing a process of myocardial hypertrophy and remodeling. Cardiac hypertrophy is characterized by a thickening of the left ventricular myocardium that is accomplished by an increase in mass and cross-sectional area of individual myocytes. Although it may initially be compensatory, cardiac hypertrophy can eventually result in decreased contractility and increased wall stress. Changes in the morphological and functional properties of the myocardium ultimately require reprogramming of cardiomyocyte gene expression. Therefore a complete understanding of mechanisms that mediate progression of heart disease requires elucidation of the signaling pathways linking cardiac contractility with reprogramming of cardiomyocyte gene expression. (page 2 of Nicol).
12. Nicols further states that the program activation in the nucleus that results in the hypertrophic phenotype is unclear (page 24 of Nicol).

13. Thus the compensatory nature of the heart to increase blood flow to the body in hypertrophic conditions, by increasing cell number (ie cardiomyocyte proliferation) and

contractile function, results in heart failure. Furthermore, Nicol teaches that the mechanistic pathways which cause the initial compensatory responses of the heart to become pathogenic responses are unclear, unknown and require additional research.

14. Patel, as stated earlier, teaches that safety of an adenoviral methodology of gene transfer in animals is complex, and does not necessarily equate with success in humans. His method produced inflammation and necrosis, and high levels of adenovirus were toxic.

15. Taking the teachings of Nicol that hypertrophic cardiomyopathies are complex and the mechanisms underlying the pathogenesis are unknown, and Patel's work on the complexities of adenoviral administration to the myocardium, further with applicant's own post-filing work, stating that over expression of the cyclin D and Cdk4 constructs results in hypertrophic myocytes in vitro, results in an unpredictable state of the art.

16. 4) Number of working examples. Applicants have provided a lone example of an injection of adenoviral vectors encoding a cyclin D1/NLS gene and a cdk4 gene into the apex of the heart of a rat by thoractomy. Applicants assess positive "proliferation" by measuring the expression of Ki-67, a proliferation marker 4 days after injection (see example 4). Applicants have not provided how many hearts were analyzed, nor an analysis if there was an actual increase in cell number or density in the cyclinD1/nls and cdk4 injected hearts in vivo. Applicants do not provide any data on the concentration of the adenovirus injected. Applicants do not use multiple concentrations of adenoviruses. Since the animals were injected with an exposed chest cavity, it is presumed that the rats were being treated with an antibiotic at the time the hearts were harvested.

Applicant provides no histology on the presence of necrosis or apoptosis in the treated myocardium. Applicant provides no immunology studies or TUNEL staining on the presence of necrosis or apoptosis in the treated myocardium. Applicants do not assess the treated hearts by echocardiography. Applicants only treat a single animal model, and provide no data on how to adjust that for any other in vivo model.

17. 5) Amount of direction or guidance present. The applicants provide generic information on in vivo administration of adenoviral and viral vectors. They do not provide detailed analysis of how to assess known problems associated with adenoviral administration to the heart (such as inflammation and necrosis). Applicant's only provide the administration of the adenoviral vectors in a single animal model, and do not teach how to alter the methodology to other animals. Additionally, applicants only administer the adenoviral vectors to healthy hearts. Applicants do not address how to alter the administration of the adenovirus for other cardiovascular disease states that might benefit from increased proliferation of cardiomyocytes (coronary artery disease, myocardial infarct, dilated cardiomyopathy, ARVD etc.). Applicants do not provide teachings that would enable a skilled artisan to make and use the claimed invention in any in vivo setting.

18. 6) Level of skill in the art. The level of skill is high. Because applicant's only provide basic information of in vivo applications for the claimed invention, the skilled artisan would be forced to perform trial and error in order to practice the claimed invention. The skilled artisan would have to investigate different animal models to look at the efficacy of the vectors in other in vivo settings, test additional concentrations,

assess cytotoxicity, and long term expression of the transgene, and analyze long term proliferation problems that might result in unregulated proliferation of the cardiomyocytes due to unrestricted expression of the transgene.

19. 7) The breadth of the claims. The breadth of the claims are broad. The claims read on a method of gene therapy by administration of any viral vector to humans.

20. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1, 4, 18, 21, 23, and 24, are rejected under 35 U.S.C. 102(b) as being anticipated by Soonpaa et al (Cyclin D1 overexpression Promoter Cardiomyocyte DNA synthesis and Multinucleation in Transgenic Mice. Journal of Clinical Investigation, 1997: 99(11):2644-2654). Claims read on a method for proliferating cardiomyocytes

comprising introducing a mammalian D1 cyclin and mammalian Cdk4 kinase into the nucleus of the cells, and cultivating or holding the cells.

23. Soonpaa teaches the generation of transgenic mice that overexpressed cyclin D1 in the myocardium, which resulted in a concomitant increase in CDK4 levels in the adult myocardium (see abstract). Cyclin D1 and Cdk4 are inherently known to form a complex and translocate into the nucleus when activated (see above), thus in overexpressed CyclinD and increase in cdk4 would be introduced into the nucleus of the cardiomyocytes of the transgenic mice. Soonpaa teaches, "hemocytometer cell counts of dispersed cell preparations revealed an approximately twofold increase in the total number of cardiomyocytes in 14-d-old transgenic mice as compared to their transgenic littermates" (page 2651 second column). Thus Soonpaa teaches the claimed invention.

Response to Arguments

24. Applicant's arguments filed 7/06/07 have been fully considered but they are not persuasive. In response to the 112 1st enablement rejection applicants traverse the rejection. Applicants point to and summarize an attached 1.132 declaration provided by Uichi Koshimizu, and argue that the Examiner was incorrect in stating that the applicants only taught a single viral vector.

25. The examiner will address the 1.132 declaration in a separate section. In response to Applicant's assertion that in the advisory action of 3/30/07 the examiner

stated that the applicants only taught a single adenoviral vector, the examiner disagrees. The advisory action dates 3/30/07 states:

26. Applicants also point out that current claim 6 limits the method to adenoviral vectors (see applicant's response dated 3/6/07). This however, does not address the issue of the type of vector used in base claims 1 and 2, which still read on a method for the proliferation of cardiomyocytes using any vector. Applicants only show and teach their method utilizing adenoviral vectors. Thus the claims which are not limited to in vitro work and adenoviral vectors are not in condition for allowance.

27. The examiner was referring to the actual reduction to practice of the examples of the specification, not that applicants did not teach any other examples of viral vectors. The examiner agrees that the specification teaches a generic listing of other viral vectors that one would use with the expression constructs (paragraph 0046 of the instant specification). However, applicants have not provided how to alter their methodology to successfully utilize the additional viral vectors: different viral vectors infect different cell types, some viruses integrate into the genome, some do not, etc. The resulting effect on the transcription, and ultimately success resulting in "proliferating cardiomyocytes" is still not addressed by applicant. Thus the claims were, and are still properly rejected under 112 1st for lack of enablement.

28. The declaration under 37 CFR 1.132 filed 7/06/07 is insufficient to overcome the rejection of claims 1-2, 4, 6, and 16-31 based upon lack of enablement as set forth in the last Office action because: the statements of Dr. Koshimizu do not address the issues remaining in the enablement rejection, as stated in the previous advisory action,

and those included with the enablement rejection over claims 1-2,4,6, and 16-31.These issues, dealing with lack of enablement for any in vivo situation (humans versus mouse versus pig versus rat), or the potential ill effects of unfetterd viral administration of the cyclin D1 and ckd4 are not addressed by Dr. Koshimizu. Dr. Koshimizu states "to confirm the effect of the expression of D1NLS + CDK4 gene on the proliferation of cardiomyocytes in vivo, and that such gene expression in vivo has a therapeutic effect on damaged cardiomyocytes, an experiment was performed using a rat myocardial ischemia and reperfusion model" (page 5 of Dr. Koshimizu's declaration). Dr. Koshimizu then goes onto describe a single experiment, on apparently a single rat (with a control rat (sham) group), wherein a single adenoviral concentration is administered directly to the infracted area and periphery of the infracted area of the myocardium, for a total of 5 injection sites. Dr. Koshimizu teaches that the hearts are analyzed for cardiac muscle troponi T in plasma to assay for necrosis, and immunohistological sections of he heart at 4 and 7 days were treated with antibodies for Troponin I, Tropomyosin, Ki-67, phosphorylated Histone H3, Aurora B, and Survivin. Dr. Koshimizu teaches that the adenovirus LacZ vetor was capable of infecting 5% of cells in the infarct zone, and that Ki-67 postitive cells were 1.95% in the D1NLS group. Dr. Koshimizu teaches that the myc tag is indiciative of the expression of the D1NLS, and he compared the myc expression to the Ki-67 cells. Thus these cells would seem to be Ki-67 as a direct result of the Di cyclin expression.

29. Interestingly, Dr. Koshimizu teaches, "Proportions of Ki67 positive cells in myc-tag positive cells were 48%." Thus only about half of the myc positive cells (the total

cells that are expressing exogenous D1NLS) are "proliferating. He does not provide data on the total number of Ki-67 cells in the treated D1NLS mice that do not also express the myc tag: an indication that proliferation is naturally stimulated in ischemic/reperfusion conditions. He does teach that the control group comprises 0.1% Ki-67 staining, nor does he state that the difference results in a statistical difference between the two groups. Thus this indicates that there is some degree of proliferating in the control group, as a natural result of ischemia/reperfusion injury in the myocardium.

30. Dr. Koshimizu further teaches that the D1NLS treated groups stain positive for H3P, Aurora B and survivin, markers of cell division. Hp3 was identified in .024 percent of cells, and 0 % for the control group. He does not provide the data for the differences between Aurora B and Survivin staining between the D1NLS and the control group. From this, Dr. Koshimizu concludes that D1NLS + CDK4 gene expression in vivo cause cell division of adult cardiomyocytes in situ to generate new functional daughter cells.

31. Echocardiographic data on treated rats six weeks after treatment :

32. Echocardiographical analysis revealed that LVDD, LVDF, and FS of the Cont/LacZ group was smaller than that of the Sham group. By contrast, FS of DINLS group was significantly higher than that of the Cont group, suggesting that the expression of DINLS+CDK4 expression protected ischemic hearts from left ventricular dysfunctioning (Table 1). In addition, in D1NLS group, the "fractional area change of left ventficular," which was used as an indicator of the systolic function, was at larger values than in the Cont group. In DINLS group, the "E/A value," which was calculated from left

ventricular blood flow influx at early diastolic stage (E) and atrium systolic stage (A) by Doppler method, was not statistically significant, but apparently smaller than in the Cont group (Sham group: 2.30 ± 0.25, Cont group: 5.49 _ 0.86, DINLS group: 3.69 - 0.68: n = 9 to 12). Table 1:

Table 1. Echocardiography at 6 weeks after reperfusion.

Group	Sham	LacZ	DINLS
N	10	11	12
LVDD (mm)	9.2 ± 0.2	12.7 ± 0.2*	11.5 ± 0.2*†
LVDS (mm)	6.0 ± 0.3	11.3 ± 0.2*	9.6 ± 0.3*†
Fractional Shortening (%)	34.8 ± 1.5	11.3 ± 0.9*	16.6 ± 1.7*†
HR (beats/min)	242 ± 6	224 ± 5	240 ± 8

Echocardiography at 6weeks after reperfusion. Each value indicates Means ± SEM. *p<0.05 vs. sham, †p<0.05 vs. LacZ.

33.

34. The examiner disagrees with the conclusionary statement by Dr. Koshimizu, that the D1NLS + CDK4 treatment protected ischemic hearts from left ventricular dysfunction. Looking at table 1, The D1NLS group also still has significant cardiac dysfunction compared to the Sham group, with larger end diastolic, end systolic, and a fractional shortening of approximately half of the control sham group. Thus these mice have lent ventricular dysfunction at 6 weeks post treatment. Furthermore, Dr. Koshimizu states that there was no statistical difference between the E/A ratio of the LacZ and N1NLS heart (section 22 of Dr. Koshimizu's declaration), The E/A ratio, as Dr.

Koshimizu explains is an indication of systolic function: thus the LacZ hearts and the D1NLS hearts had no difference in systolic contractile function.

35. Dr. Koshimizu also states that the Lacz group develops heart failure at 6 weeks, as indicated by dp/dt values, LVEDP, LVEDV and pressure-volume curves, and "Theses parameters were greatly improved in the D1NLS group as compared to the Control Group." However, Dr. Koshimizu does not provide the data on the D1NLS mice, and thus, these hearts could also be in heart failure according to these models, however the degree of heart failure may be different. But without the data to analyze, the Examiner does not agree that the hearts of the D1NLS mice are "greatly improved."

36. Dr. Koshimizu also states that the infarct area of D1NLS heart was significantly reduced.

37. Dr. Koshimizu states, "based on the above results, it was confirmed that the introduction of an adenoviral vector comprising a D-type cyclin and cyclin dependent kinase gene into cardiomyocytes in vivo proliferates the cardiomyocytes. Furthermore, based on the above results, it was confirmed that expression of D1NLS and CDK4 genes has protective effects on cardiac dysfunction and heart failure. In my opinion a person of skill in the art would understand that the '008 application teaches one of skill in the art to carry out a method for proliferating cardiomyocytes introducing an adenoviral vector comprising a D-type cyclin and cyclin dependent kinase gene into cardiomyocytes."

38. The examiner respectfully disagrees. Dr. Koshimizu provides no additional evidence in the examples of rat hearts provided in the declaration that the methods of

the instant specification are applicable to other forms of in vivo work. In reality, the protocol of the administration of a rat heart ischemic model is not mentioned in the instant specification, nor is the administration of the adenoviral vector in 5 different locations in or near the infarct zone, found anywhere within the body of the instant specification. Furthermore, Dr. Koshimizu demonstrates that there are some differences between the D1NLS hearts and the lacZ heart, but that overall systolic function as assessed by E/A ratios of the hearts, as measured by echocardiography is not statistically different. Dr. Koshimizu alludes to the rat hearts having improved values in heart failure compared to control, but does not actually say that the hearts are not also suffering from heart failure.

39. Dr. Koshimizu does not point to the specification where one might find the teachings of the administration of the instant invention to other animals, or if the specification teaches how to adjust the methodology for different species. The concentrations for the administration of the adenoviral vector that Dr. Koshimizu uses is not described in the specification. Is that considered common knowledge? How would the methodology be changed for different forms of cardiovascular disease? In a patient suffering from ARVD, where the cardiac tissue is replaced by fatty tissue, where would the adenovirus be administered? How does Dr. Koshimizu adjust the protocol in hearts suffering from other forms of cardiomyopathies? How would the protocol be adjusted for utilizing other viral vectors? Does it get adjusted by what type of disease is being treated, or the animal being treated? Or both? To what extent? How?

40. Thus, in conclusion, the declaration provided by Dr. Koshimizu is insufficient for overcoming the 112 1st enablement rejection of the prior advisory action, and repeated herein.

41. Conclusion

42. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/09/11/07

/Daniel M. Sullivan/
Primary Examiner
Art Unit 1636